

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

## **Alterations of Nutritional Status in Childhood Acute Leukemia**

---

Alejandra Maldonado-Alcázar,  
Juan Carlos Núñez-Enríquez,  
Carlos Alberto García-Ruiz,  
Arturo Fajardo-Gutierrez and  
Juan Manuel Mejía-Aranguré

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/52715>

---

### **1. Introduction**

Nutritional status is the result of the interaction between environmental and genetic conditions in which a child lives, when these environmental conditions are favorable for life (physical, biological, nutritional and psychosocial), the genetic potential is expressed as an ideal state of nutrition, but when conditions are unfavorable such expression will be diminished, resulting in altered nutritional status, such as malnutrition, overweight and obesity, which among other things would cause the child did not respond to a disease or its treatment suitably at a given time. [1]

In different studies conducted in children with cancer, the authors have evaluated the impact of nutritional status, assuming that if a cancer patient is well nourished, have less toxicity caused by antineoplastic drugs, will have a greater immune resistance to processes serious infectious, and therefore have a better survival and quality of life than the patient who is not well nourished, so in this chapter we will mention the most important conclusions that have been made with respect to this issue. [2]

Malnutrition is the main nutritional disorder that occurs in children with cancer, and has been defined as a state in which a deficiency of energy, protein, and other nutrients, causes measurable adverse effects on the structure and functioning of organs and body

tissues as well as the clinical course of a disease. In order to explain the mechanisms by which it causes malnutrition in children with cancer, three factors have been proposed: a) factors specific to the tumor (tumor growth factors released by the tumor cells as bombesin and adrenocorticotrophic hormone) b) factors related to the patient (pediatric age, low socioeconomic status, poor nutrient intake, increased secretion of growth hormone and cytokines that are released by the body in response to tumor growth, among the most important are the tumor necrosis factor, interleukins 1 and 6), and last but not least, c) factors related to the treatment (type / dose of chemotherapy, site / dose of radiotherapy and surgery). It is also suggested that all these factors would cause an alteration in intermediary metabolism, with resultant decrease in appetite, which eventually lead to the patient to lose weight, creating a vicious cycle. [2-6]

### **1.1. Prevalence of malnutrition in children with cancer**

It has been reported that children with cancer will develop signs and symptoms of malnutrition at some point in the disease by up to 50-60% of cases, however, this frequency may vary according to the type of neoplasm, and according to if the study was conducted in developed countries or in developing countries, where there has been an increased frequency of nutritional alterations. It should be mentioned, that the study of the prevalence of malnutrition in children with cancer is mainly determined by whether it is present at diagnosis, this is important because it also could establish their potential impact on the evolution of these patients before treatment started. [7,8]

In this regard, Brinksmma A, et al., (2012) reported the prevalence of malnutrition at diagnosis for developed countries, through a systematic review which included patients with different types of childhood cancer, aged from 0-18 years of age for acute leukemias, the prevalence was 10%, 20-50% for neuroblastoma, and those classified as "other malignancies" was 0-30%, these prevalences are low when compared with those that have been estimated for developing countries where they are as high as 50% for all types of childhood cancers. [2,8,9]

## **2. Nutritional status assessment in children with acute leukemia**

There are several clinical, biochemical and physiological indicators to diagnose malnutrition in children with cancer; such as the patient's age, the deficit of specific micronutrients and the presence or absence of infection. The severity of their malnutrition is determined mainly by anthropometric indicators, that are the indexes of weight-for-height (w/h) and weight-for-age (w/a), which indicates acute malnutrition (table 1), height-for-age (h/a) which indicate a delay in growth or chronic malnutrition; and the Body Mass Index (BMI), which is a figure that can diagnose a patient for being underweight, overweight or obesity. [10,11] (table 4)

Percentile	Diagnosis
<5	Malnourished
5-85	Normal
> 85 a < 95	Overweight
≥ 95	Obesity

**Table 1.** Diagnosis by percentile for the indexes weight-for-height, weight-for-age based on the World Health Organization (WHO) tables.

Waterlow’s Classification:

Denomination	Index	Classification
Wasting	Weight-for-height <5	Acute Malnutrition
Stunting	Height-for-age <5	delay in growth or chronic malnutrition

**Table 2.** Denomination of wasting and stunting with Waterlow’s classification. [12, 13]

Waterlow’s classifications:

Denomination	Index	Classification
Wasting, no stunting	Weight-for-height <5 , height-for-age Normal	Acute malnutrition
Wasting and stunting	Weight-for-height <5 , height-for-age <5	Exacerbated-chronic malnutrition
Stunting, no wasting	Weight-for-height Normal, height-for-age <5	Chronic malnutrition

**Table 3.** Combinations of nutritional diagnosis with Waterlow’s classification. [12,13]

Percentil	Diagnosis
<5	Underweight - Malnourished
≥5 y <85	Normal
≥85- <94	Overweight
≥95	Obesity

**Table 4.** Diagnosis by percentile for the Body Mass Index (BMI) based on the World Health Organization (WHO) tables [10]

It's important to consider the body composition in children with cancer, with which we are able to determine the quantity of lean mass and body fat in their bodies, in order to see if there is muscular depletion. The anthropometric measures used to get body composition can be the Mid Upper Arm Circumference (MUAC), triceps (TSF), biceps, subscapularis and suprailiac skinfolds; [14] and in case of having the necessary equipment, the use of electric bioimpedance or D-XA (Dual X-Ray Absorptiometry) is recommendable.

With the mid upper arm circumference and the triceps skinfold, you can calculate the muscle and fat area by using the following formula:

Then comparing the score with the Frisancho tables where:

Percentile	Diagnosis
0 – 5	Wasted
5.1 – 15	Below average
15.1 – 85	Average
85.1 - 95	Above Average
>95	High muscle

**Table 5.** Diagnosis by percentile for upper arm muscle area based on Frisancho tables. [14]

Aside from those anthropometric indicators, there are biochemical indicators that are used to diagnose protein malnutrition, like albumin and pre-albumin which are the most important due to their hepatic synthesis, and total protein. [15,16]

The half- life of albumin is 20 days, therefore it can assess acute malnutrition and can be used as a morbidity and mortality prognosis factor.

Reference value	Diagnosis
3.5 - 5.5 g/dl	Well-nourished
2.8 - 3.5 g/dl	Malnourished Grade 1
2.1 - 2.7 g/dl	Malnourished Grade2
< 2.1 g/dl	Malnourished Grade 3

**Table 6.** Albumin reference values and diagnosis [15]

Prealbumin has a 2 days half life wich means it is a very sensible marker for acute malnutrition, but the result may be affected by inflammatory reaction, therefore is not useful to track changes on the nutritional status unlike albumin that can be a better marker for protein malnutrition. [16]

Reference value	Diagnosis
17 - 42 g/dl	Well-nourished
<17 g/dl	Malnourished

**Table 7.** Prealbumin reference values and diagnosis [17]

It is important to make a full assessment of nutritional status in these children as this can influence the patient's response to the treatment.

### 3. Impact of malnutrition in Acute Lymphoblastic Leukemia (ALL)

The study of the impact of malnutrition in children with cancer has been conducted primarily in patients with acute leukemia, specifically in (ALL) perhaps because it is the most common type of cancer in children worldwide. [18-21] In two papers published one by Underzo et al., and in another by Reilly J, et al., reported that the prevalence of malnutrition at diagnosis in patients with ALL was 7% for developed countries, and on the contrary, in different studies conducted in developing countries have reported higher prevalence of up to 21-23%, which confirms the statement that in countries with low economic development, malnutrition occurs more frequently, This could be a result of poverty. It is for this reason that for several years, these countries have made efforts to determine the true impact of malnutrition as a prognostic factor in patients with acute leukemia in children at different stages of treatment. [22-25]

#### 3.1. Prognosis

As is known chemotherapy used in the treatment of patients with ALL has some serious effects that may endanger the life of patients at a given time. Among the most common side effects of QT are toxicity to various organs, infection, hemorrhage, tumor lysis syndrome (TLS), among others., which would be the cause of high morbidity and mortality. It is for this reason that the current chemotherapy protocols in children with ALL are based on a risk classification to reduce toxicity in low-risk patients as well as ensure that therapy is adequate and aggressive to those classified as high risk. [26,27]

In the group of patients with ALL who are malnourished at diagnosis, it was found that chemotherapy is more toxic and less effective compared to those found with adequate nutritional status, specifically haematological toxicity is the cause of most complications, such as an increased risk to present infections, bleeding and an increased risk of relapse, the above due to neutropenia, thrombocytopenia, and discontinuation of treatment, respectively.

The main effect of malnutrition on treatment, is due to an alteration of the biodisponibility of antineoplastic drugs, which is achieved through the following mechanisms: a) changes in absorption, eg for drugs like methotrexate and 6 mercaptopurine, b) the decreased drug

transport by the reduction or lack of plasmatic proteins, and c) by decrease in hepatic metabolism of the antineoplastic mainly caused by a lack of enzymatic activity by cytochrome P450. [28-37]

Furthermore, highlight the importance of studying on the subject of how malnutrition affects the prognosis of patients with ALL, because in some of the studies did not allow conclusions to determine whether the association exists in some of these studies were given the limitations by factors such as inadequate sample size, the inconsistency in how to assess the nutritional status between studies, and also have not been studied other possible complications in the evolution of these patients, such as relapse, abandonment in the treatment, among others. [28,38-40]

### 3.2. Survival

Moreover, since 1980 the rates of event-free survival has improved in patients with ALL, currently reported survival at 5 years is 80% and 10-year survival is 60% in developed countries, however, in developing countries cure rates are less than 35%, so on a quest to determine the factors related to mortality in developed countries, but mainly in developing countries, has been studied by different authors on the role of malnutrition on survival of patients with ALL; remain controversial until now because while on the one hand, some authors have reported that survival rates are lower in malnourished patients compared with patients who are well nourished and of the same risk, in other studies, it has not been possible to confirm this association. [8,29,41] According to Reilly J, et al., There are three mechanisms that explain the direct influence of malnutrition on survival of patients with ALL: The first, means that if there is a greater severity of malnutrition, there will be a greater severity of leukemia this because as we know, malnutrition is a surrogate marker of the disease state, the second mechanism is related to immune system dysfunction that occurs in malnourished patients, which would cause increased susceptibility to potentially serious infections could lead to the death of the patient, and finally, a mechanism related to adipose tissue, which has as one of its main functions being a facilitator to take place the pharmacokinetics of many anticancer drugs, this tissue is functionally and structurally altered in malnutrition, resulting in a lower effective antineoplastic drugs and greater toxicity and that both could be potential factors sufficient to endanger the patient's life, however this mechanism has been studied by other authors who found no such effect. [23-39]

Therefore, it is believed that malnutrition alone is a major factor in poor prognosis and survival of patients with ALL, however, it is noteworthy that most of the studies performed, are from developed countries and / or where it is mainly evaluated the impact of malnutrition on long-term survival, so it is necessary to know whether the association also exists in developing countries, because these populations have certain characteristics, such as frequencies malnutrition and deaths occur primarily during the first year of treatment much higher, and it also has been reported as one of the main obstacles to improved survival rates in patients with ALL. [39,42-45]



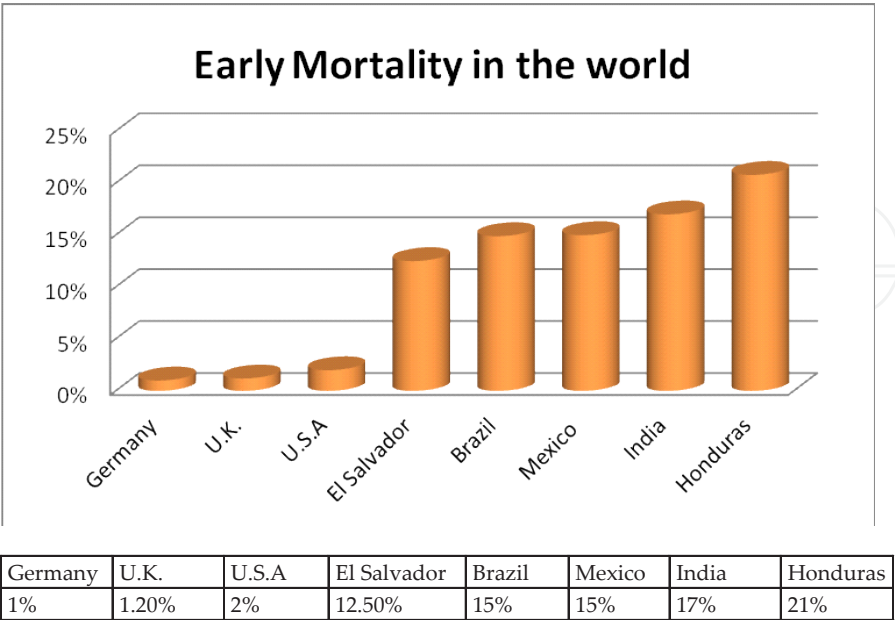
3.3. Malnutrition and early mortality

Early mortality can be defined as death during the first year of treatment, and it includes treatments as chemotherapy of induction to remission, central nervous system prophylaxis and consolidation. In several cases around the globe, the early mortality rate for developed countries is significantly lower than the one presented in developing countries. Main causes for early mortality include complications during chemotherapy treatment, such as infections, hemorrhages and toxicity, since their presence often represent an interruption in the treatment.

A 1999 study conducted by Silverman and collaborators in the Dana-Farber Cancer Institute, United States; a mortality rate of 2% in the first stage of treatment was reported, mainly caused by infections. [46] Another study conducted in the UK in 1997 also measured the rate of early mortality in these patients, reporting a mortality rate of barely 1.2%, with infections still being the main cause of death; however, cases of brain hemorrhage and tumor lysis syndrome (TSL) were also detected. [47]

The country that reports the lowest percentage of mortality in early stages of treatment is Germany, which reported only a 1% death rate in their patients between 1984 and 1996; with most of the deceases caused by hemorrhages and tumor lysis. [41]

While that’s the case in developed countries, where very low mortality rates are reported; a study conducted by Rivera Luna and collaborators in Mexico’s Instituto Nacional de Pediatría (INP) threw results of a 15% mortality rate during the phases of induction to remission. [37] In other developing countries like Honduras, El Salvador, Brazil, and India mortality also shows a spike in rates compared to developed countries, with an early mortality rate of 20.8%, 12.5%, 14.9% and 17% respectively, as you can see in Graph 1. [48-51]



Graphic 1. Incidence of early mortality in patients with ALL around the world.



A possible explanation for this marked difference might be that malnutrition, poverty and lack of access to public health services are frequent problems in developing countries, unlike developed countries where children with leukemia have lower early mortality rates.

There have been several studies that try to correlate malnutrition with the evolution of patients with ALL. The first one was conducted in Mexico in 1989 by Lobato Mendiazabal et al., where there's a categorization of children with or without malnutrition based on weight-for-height indicators. It was found that, when measuring 5 year survival rate, 80% of children without malnutrition survived, while patients with malnutrition had a survival rate of barely 26% in the same period. [44]

As far as early mortality and relapses during the first year of treatment go, only 4% of children diagnosed with good nutrition suffered any of those events, while 63% of ill nurtured children experienced a relapse or death. This study was conducted in Puebla, with a sample size of 42 children of a single hospital facility (Hospital Universitario de Puebla). [44]

In a case and control study conducted by Mejia Arangur  and collaborators the state of nutrition of several patients with the weight-for-height indicator was tested and compared for diagnosis with the boards of Federico G mez. For this study 93 cases of 2 hospital sources were taken; Hospital Infantil Federico G mez and Hospital de Pediatr a de Centro M dico Nacional S XXI. [35]

It was found that children with malnutrition at the moment of diagnosis were almost 2.6 times more likely to die in comparison to children without malnutrition. Therefore, it was concluded that malnutrition is a factor that increases the mortality rate of children with ALL, and an association directly proportional to the severity of the nutrition was established. [24]

In a prospective cohort conducted in 63 patients by Khan and collaborators, malnutrition was classified with the index of weight-for-height, and the result was that 46% of children with malnutrition at the moment of ALL diagnose completed their treatment; only 9.8% suffered a relapse and 45% died; meanwhile children without malnutrition experienced a 59% survival to their treatment, a 21% relapse rate and 19% died. Thus, malnutrition was considered as a bad prognosis factor for children with ALL. [36]

One of the most recent studies was conducted in Bangladesh by Hafiz MG and collaborators in 2008. This study only takes a sample of 66 patients from the Indian Pediatric Hospital, the index they used was the weight-for-height measurement, although they don't specify the tables that results were compared to in order to classify the state of nutrition.

They concluded that children that present malnutrition have 2 to 3 times the risk of infection in comparison to children without malnutrition. It was also observed that children with malnutrition needed more time for induction therapy since their dosage has to be lowered, or their treatment was interrupted for toxicity. [28]

Another study realized by Pedrosa F. and collaborators in 2000, took in account indicators as weight-for-height, height-for-age and weight-for-age; comparing them to WHO data. For this study they took in account patients with any type of leukemia and patients with solid tumors. This study was collaboration between two hospitals in El Salvador and Brazil, where they were able to include 443 patients. Of that number, 151 had an ALL diagnosis. At the beginning of the study children were classified as children with malnutrition and children without malnutrition, and children with malnutrition were provided with a dosage of albumin 2 weeks before starting chemotherapy. The study concluded that “malnourishment doesn’t have a relevant association with these patients’ survival”. [38]

The most recent study published on this subject was conducted with patients of Mexico’s Instituto Nacional de Pediatría, with 100 patients diagnosed with ALL. Their state of nutrition was determined with indicators of weight-for-height and height-for-age and compared to the NHANES tables of the CDC in the United States. This was a retrospective study where the follow up was done during the phases of induction to remission, and the results were as follow: 14.9% of children without malnourishment died during treatment phase, while 5.1% of patients without malnourishment perished in this stage of treatment Therefore, it was concluded that malnutrition didn’t play an important role in early mortality in children with ALL. [37]

In a retrospective cohort done in El Salvador with 469 patients, besides BMI index, triceps skinfolds and Mid Upper Arm Circumference were taken into consideration. This study concluded that malnourishment had no association with mortality during treatment. [49]

A study conducted by Hijiya and collaborators demonstrated with a retrospective cohort of 621 patients of St. Jude’s Hospital in United States concluded that BMI didn’t affect the evolution of patients with ALL. This study took BMI as the main nutritional indicator and divided children in 3 groups: malnourished, normal and obese. The survival rates in these categories were similar, children with malnutrition presented a survivability rate of 86.1%, children with a normal nutrition state had an 86% survivability rate and in obese children the figure was of 85.9%. [39]

There’s controversial information about the relationship between the effects of malnutrition in the evolution of patients with ALL, mostly because even with a wide range of studies, some conclude there’s a significant relation between these factors [24,28,44] while others conclude that there’s no relation. [37-39, 49]

One of the reasons is the bias in the classification of malnutrition, since in some studies like Pedroza and collaborators [38] the World Health Organization (WHO) charts are used, and in Rivera Luna and collaborators [37] they used the charts of the National Health and Nutrition Examination Survey (NHANES), while in the study conducted by Lobato Mendizabal and collaborators the charts of Ramos Galván were taken into account [44] and at last the study of Mejía Aranguré and collaborators used Federico Gómez’ charts. [24]

In the studies mentioned, the sample was taken only from one or two hospital sources, so it’s important to conduct a multicentre study that can show a wider panorama of the effects of malnourishment in the evolution of children with ALL.

<b>Autor (Year)</b>	<b>Lobato Mendiazabal et al. (1989)</b>	<b>Mejía Aranguré et al. (1999)</b>	<b>Pedrosa F. et al. (2000)</b>	<b>Rivera Luna et al. (2005)</b>
Country	Mexico	Mexico	El Salvador and Brazil	Mexico
Hospitals	Centro de Hematología Medicina Interna and Hospital Universitario de Puebla	Hospital de Pediatría S. XXI and Hospital Infantil de México Federico Gómez	Hospital de niños Benjamín Bloom and Instituto Materno-Infantil de Pernambuco	Instituto Nacional de Pediatría
Type of study	Prospective cohort	Case- control	Retrospective Cohort	Retrospective Cohort
Sample size	43 patients	93 patients, 17 cases and 76 controls	443 patients 151 with ALL	100 patients
Age	1-15 years	<16 years	0-17.8 years	0-15 years
Parameters used	Weight-for-age	Weight-for-height	Weight-for-age, Height-for-age Weight-for-height	Height-for-age, Weight-for-height
Classification	Ramos- Galvan's Tables	Federico Gómez Tables	WHO's Tables	National Health and Nutrition examination survey NHANES
Results	5-year survival in well nourished versus malnourished patients: 83% in well nourished Vs 26% in malnourished. Death and relapses: 4% in well nourished vs. 63% malnourished. Reduction of chemotherapy treatment: 75% in well nourished Vs. 56% malnourished.	Children who had malnutrition at the time of diagnosis were 2.6 more likely to die than children without malnutrition; therefore malnutrition increases mortality in children with LLA.	Malnutrition has no association with survival of patients Note: A dose of Albumin was applied to malnourished children 2 weeks before they started treatment.	14.9% of well nourished children died during the induction to remission therapy; 15.1% of malnourished children died during the same stage of treatment, "Malnutrition does not play a role in early mortality in children with ALL".
Country	USA	Pakistan	Bangladesh	El Salvador
Hospitals	St. Jude's Children Research Hospital	Shaukat Khanum memorial Hospital	Pediatric Hematology and Oncology	Hospital de niños Benjamín Bloom
Type of study	Retrospective cohort	Prospective cohort	Prospective cohort	Prospective Cohort
Sample size	621 patients	163 patients	66 patients	469 patients

Autor (Year)	Lobato Mendizabal et al. (1989)	Mejía Aranguré et al. (1999)	Pedrosa F. et al. (2000)	Rivera Luna et al. (2005)
Age	1-16 years	<14 years	1-15 years	0-16 years
Parameters used	BMI	Weight-for-height	Weight for age	BMI, MUAC,(TSF)
Classification	CDC tables	Waterlow`s Classification	Not specified	CDC Tables
Results	Children were divided in 3 categories: <10° malnourished; >ó= 85° well nourished; > 85 < 95° overweight; >95 Obesity; Note: Chemotherapy dosage was not adjusted by BMI. Survival rate: 86.1%, 86.0%, 85.9% and 78.2% respectively BMI has no effect on the survival of LLA children.	Malnourished children: 46% complete treatment and were alive, 9.8% relapse and 45% died. Well nourished children: 59% complete treatment and were alive, 21.3% relapse and 19% died. " Malnutrition is a prognosis factor in LLA children"	Malnourished children are 3 times more likely to present infections tan well nourished ones. Malnourished children need more time of induction to remission treatment due to the dose reduction caused by toxicity.	Malnutrition has no association with early mortality in children with LLA.

**Table 8.** Studies about the effect of malnutrition at time of diagnosis and early mortality in children with ALL.

**4. Overweight and obesity in survivors of childhood acute lymphoblastic leukemia**

Concern about children who suffered from ALL is the long-term consequences that therapy may bring after the leukemia has been overcome. Various studies have shown that nutritional abnormalities like obesity and overweight are commonly found in ALL survivors, with a prevalence of 20-34% depending on the country where it has been studied. [52,53]

van Waas et al, conducted a study in 2004 in the Netherlands during the period from 2002 to 2007 in a single-center cohort of 500 survivors of childhood ALL. The ages of these patients at the time of the study ranged from 18 to 59 years, of which 288 were females and 212 were males, measured variables corresponded to the levels of total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, BMI, and the authors finally concluded that patients who had been treated with cranial radiotherapy (CRT) had a higher frequency of overweight (59% versus 34%, P = 0.003) than those who had not received CTR. [54]

Obesity and overweight are defined as the result of varying degrees of abnormal or excessive accumulation of fat. The World Health Organization defines overweight as a BMI of 25 to 29.9, and obesity as a BMI of  $\geq 30$ . The BMI modifications in survivors of childhood ALL are noteworthy because they are associated with insulin resistance, diabetes mellitus, hypertension, dyslipidemia and with an increased cardiovascular risk. [55]

#### **4.1. Mechanisms involved in the development of overweight and obesity in ALL survivors**

Because of this, the processes by which these nutritional abnormalities are developed by ALL survivors are being studied, though the exact mechanisms are still uncertain, nonetheless, there are some hypotheses that would explain metabolic deregulations leading to the development of altered BMI by the excessive accumulation of body fat. Here we will focus on the effects due to radiotherapy and corticosteroids. However, it is important to point out that exist other factors linked to these alterations. For example, long hospitalization periods because of immunosuppression or vincristine-induced peripheral neuropathy may cause restricted physical activity in these patients. In addition to this, it should not be left out the usual risk factors for developing obesity of each population. [56]

##### *4.1.1. Effects attributed to cranial radiation therapy*

In one of the largest studies conducted so far related to the effect of radiotherapy for the development of overweight and obesity in ALL survivors by Oeffinger et al, (2003), reported that the dose and radiation site were the mainly cause. This study was conducted during the period from 1980 to 1994 the study population corresponded to 1765 cases and 2588 controls aged 18-42 years old. Considering a radiation dose greater than 20Gy there was a risk factor for obesity in men with an OR 1.86 for illness (95% CI, 1.33 to 2.57,  $P < .001$ ) and in women with an OR of 2.59 (95% CI, 1.88 to 3.55,  $P < 0.001$ ), without observing this nutritional disorder in patients who had received chemotherapy alone or had received cranial radiation doses of 10 to 19 Gy. [57]

Lackner H et al 1991 and subsequently by Janiszewski et al., (2007), reported that the levels of growth hormone (GH), insulin-like factor (IGF1) and leptin levels were significantly lower in CRT than in non-CRT. [58,59]

The mechanism proposed to explain the growth hormone deficiency, holds that cranial radiotherapy (CRT) given at a young age to treat children suffering from ALL, damages the hypothalamus neurons, inducing growth hormone deficiency (GHD). [60] Deficiency in the secretion of growth hormone (GH) has been associated with the augmented percentage of body fat. Evidence that supports these hypothesis are the decreased levels of IGF-1 (also known as somatomedin C), which is a mediator of the GH action in target tissues.

Apart from their individual effects, there is evidence that relates leptin and GH. GH and IGF-1 are decreased in response to fasting. Impaired GH synthesis and secretion occurs along with a leptin deficiency or abnormality on its receptor. Leptin may also regulate GH via somatostatin synthesis inhibition and secretion, allowing GH to yield its actions over the targeted tissues. [61]



Among many other physiological functions of the GH, this hormone promotes utilization of fats as source of energy, inducing the liberation of fatty acids into the bloodstream. At the same time, it has anabolic protein effects which are traduced in an increase of lean body mass. [62]

Moreover, it has been recently suggested that only susceptible individuals will develop obesity when treated with CRT. This susceptibility has been tracked down to a polymorphism in the leptin receptor in the hypothalamus. This polymorphism (Arg/Arg) was found by Ross et al., to be associated to females having a BMI  $\geq 25$ , treated with CRT. [63] Leptin is a hormone produced by adipocytes and it is involved in feeding behavior regulation and energy balance. Stored energy in adipose tissue is closely watched by the hypothalamus, through this hormone. An increase in adipose tissue will be traduced in increased leptin synthesis by adipocytes, and by negative feedback over the hypothalamus food intake will be inhibited. [64,65]

#### *4.1.2. Corticosteroid therapy*

Because corticosteroids are used to treat ALL, it is important to point out that they also promote leptin synthesis. However, conducted studies have only shown short-term effects on increasing body weight. However, these findings strongly suggest doing more research to determine if glucocorticoids induce long-term body weight via leptin synthesis or through other mechanisms. [66]

After it has been released to the blood stream, leptin reaches the central nervous system and binds to its receptors found in the hypothalamic neurons of the arcuate, ventromedial, and dorsomedial nuclei. The activation of the receptors, decreases the production of orexigenic (or appetite stimulant) substances such as neuropeptide Y and agouti-related peptide. It also activates the sympathetic nervous system, increasing the metabolic index and energy consumption. As for the insulin, leptin reduces its secretion, resulting in diminished energy storage. [62]

As it has been shown leptin insensitivity, would have repercussions in the regulation of body weight and metabolism. This leptin resistance can be attributed to abnormal receptors as well as malfunctioning intracellular signaling. [61] Either way, disruption of the leptin signaling, will eventually result in metabolic modifications that would lead to a raised BMI.

Furthermore, ALL survivors with CRT have higher risk of developing other components of the metabolic syndrome. [53] Gurney et al. encountered that ALL survivors who received CRT have increased total cholesterol levels, abnormally low HDL-C, altered triglycerides and LDL-C, compared to those who were not given CRT. [65]

## **5. Conclusions**

As it has been shown, treatment for ALL predisposes patients to suffer from obesity and metabolic alterations, not only after, but also during it. Because of this, physicians should make patients being treated for ALL and those who have overcome ALL, aware of the possi-

bility to develop these changes, and should strongly advise them to develop healthy life-styles, in order to counteract this increased risk. In addition, strict medical follow-up should be set for the early detection of this alterations, so that adequate medical intervention and/or habit shifts could take place before irreversible damage has occurred.

## Acknowledgements

This work was funded by the Instituto Mexicano del Seguro Social through its program, Apoyo Financiero para el Desarrollo de Protocolos de Investigación en Salud en el IMSS(2005/1/I/078; FIS/IMSS/PROT/PRI0/11/017).

## Author details

Alejandra Maldonado-Alcázar, Juan Carlos Núñez-Enríquez, Carlos Alberto García-Ruiz, Arturo Fajardo-Gutierrez and Juan Manuel Mejía-Aranguré\*

\*Address all correspondence to: [juan.mejiaa@imss.gob.mx](mailto:juan.mejiaa@imss.gob.mx)

Research Unit in Clinical Epidemiology, Hospital of Pediatrics, National Medical Center 21st Century, Mexican Institute of Social Insurance, (IMSS), Mexico City, Mexico

## References

- [1] Krebs NF, Primak LE., Haemer M. Normal Childhood Nutrition & Its Disorders. In: Hay WW, Levin MJ, Sondheimer JM, Deterding RR, (eds.) CURRENT Diagnosis & Treatment: Pediatrics. New York: McGraw-Hill; 2011. Chapter 10. Available from <http://www.accessmedicine.com/content.aspx?aID=6578685> (accessed August 19 2012)
- [2] Brinksma A, Huizinga G, Sulkers E, Kamps W, Roodbol P, Tissing W. Malnutrition in childhood cancer patients: A review on its prevalence and possible causes. *Critical reviews in oncology/hematology*. 2012;83(2):249-75.
- [3] Kramárová E, Stiller CA. The international classification of childhood cancer. *International journal of cancer* 1996;68(6):759-65.
- [4] Draper GJ, Kroll ME, Stiller CA. Childhood cancer. *Cancer surveys* 1994;19-20:493-517.
- [5] Reilly JJ, Odame I, McColl JH, McAllister PJ, Gibson BE, Wharton BA. Does weight for height have prognostic significance in children with acute lymphoblastic leukemia? *The American journal of pediatric hematology/oncology* 1994;16(3):225-30.



- [6] Kuvshinnikov VA. The nutritional status characteristics and the protein metabolic indices of children with acute leukemia. *Voprosy pitaniia* 1990;(3):24-8.
- [7] Tazi I, Hidane Z, Zafad S, Harif M, Benchekroun S, Ribeiro R. Nutritional status at diagnosis of children with malignancies in Casablanca. *Pediatric blood & cancer* 2008;51(4):495-8. ISSN:
- [8] Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition--A dynamic triangle in review. *Cancer* 2004;100(4):677-87.
- [9] Barr RD, Ribeiro RC, Agarwal BR, Masera G, Hesseling PB, Magrath IT. Pediatric oncology in countries with limited resources. In: Pizzo PA, Poplack DG. (eds.) *Principles and practice of pediatric oncology*. Philadelphia: Lippincott, Williams and Wilkins; 2002. p1541-1552.
- [10] Dávila-Rodríguez MI, Novelo-Huerta HI, Márquez-Solís R, Cortés-Gutiérrez E, Pérez-Cortés P, Cerda-Flores RM. [Nutritional indicators in children with acute lymphoblastic leukemia]. *Revista médica del Instituto Mexicano del Seguro Social* 2010 Nov-Dec;48(6):639-44.
- [11] Zalina AZ Jr, Suzana S, A Rahman AJ, Noor Aini MY. Assessing the nutritional status of children with leukemia from hospitals in kuala lumpur. *Malaysian journal of nutrition* 2009 Mar;15(1):45-51.
- [12] Waterlow JC. Classification and definition of protein-calorie malnutrition. *British medical journal*. 1972 Sep 2;3(5826):566-9.
- [13] Waterlow JC, Buzina R, Keller W, Lane JM, Nichaman MZ, Tanner JM. The presentation and use of height and weight data for comparing the nutritional status of groups of children under the age of 10 years. *Bulletin of the World Health Organization* . 1977;55(4):489-498.
- [14] Frisancho, A. R.; Tracer, S. P. Standards of arm muscle by stature for the assessment of nutritional status of children. *American journal of physical anthropology* 1987. 73(4):459-65
- [15] Poskitt, E. Clinical nutritional assessment. Ed in: *Practical Paediatric Nutrition*. London; Butterworth, 1988
- [16] Koskelo EK, Saarinen UM, Siimes MA. Low levels of serum transport proteins indicate catabolic protein status during induction therapy for acute lymphoblastic leukemia. *Pediatric hematology and oncology* 1991 Jan-Mar;8(1):53-9.
- [17] Ingenbleel Y, DeVisscher M, McNay T P. Measurement of prealbumin as an index of protein-calorie malnutrition. *Lancet* 1972; 2(7768):106-9.
- [18] Mejía-Aranguré JM, Bonilla M, Lorenzana R, Juárez-Ocaña S, de Reyes G, Pérez-Saldivar ML, González-Miranda G, Bernáldez-Ríos R, Ortiz-Fernández A, Ortega-Alvarez M, Martínez-García M del C, Fajardo-Gutiérrez A. Incidence of leukemias in

children from El Salvador and Mexico City between 1996 and 2000: population-based data. *BMC Cancer* 2005;5:33.

- [19] Draper GJ, Kroll ME, Stiller CA. Childhood cancer. *Cancer surveys* 1994;19-20: 493-517.
- [20] Mejía Aranguré JM, Ortega Alvarez MC, Fajardo Gutiérrez A. Acute leukemias epidemiology in children. Part 1. *Revista médica del Instituto Mexicano del Seguro Social* 2005;43(4):323-33.
- [21] Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. *Pediatric clinics of North America*. 2008;55(1):1-20, ix.
- [22] Uderzo C, Rovelli A, Bonomi M, Barzaghi A, Strada S, Balduzzi A, Pirovano L, Maserà G. Nutritional status in untreated children with acute leukemia as compared with children without malignancy. *Journal of pediatric gastroenterology and nutrition* 1996 ;23(1):34-7.
- [23] Reilly JJ, Weir J, McColl JH, Gibson BE. Prevalence of protein-energy malnutrition at diagnosis in children with acute lymphoblastic leukemia. *Journal of pediatric gastroenterology and nutrition* 1999;29(2):194-7.
- [24] Mejía-Arangure JM, Fajardo-Gutiérrez A, Bernáldez-Ríos R, Rodríguez-Zepeda MC, Espinoza-Hernández L, Martínez-García MC. Nutritional state alterations in children with acute lymphoblastic leukemia during induction and consolidation of chemotherapy. *Archives of medical research* 1997;28(2):273-9.
- [25] Delbecque-Boussard L, Gottrand F, Ategbo S, Nelken B, Mazingue F, Vic P, Farriaux JP, Turck D. Nutritional status of children with acute lymphoblastic leukemia: a longitudinal study. *The American journal of clinical nutrition* 1997;65(1):95-100.
- [26] Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, Ribeiro RC, Rubnitz JE, Raimondi SC, Onciu M, Coustan-Smith E, Kun LE, Jeha S, Cheng C, Howard SC, Simmons V, Bayles A, Metzger ML, Boyett JM, Leung W, Handgretinger R, Downing JR, Evans WE, Relling MV. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *The New England journal of medicine* 2009;360(26): 2730-41.
- [27] Pizzo PA, Poplack DG. *Principles and Practice of Pediatric Oncology*. Lippincott Williams & Wilkins;2011
- [28] Hafiz MG, Mannan MA. Nutritional status at initial presentation in childhood acute lymphoblastic leukemia and its effect on induction of remission. *Mymensingh medical journal* 2008;17(2 Suppl):S46-51.
- [29] Murry DJ, Riva L, Poplack DG. Impact of nutrition on pharmacokinetics of anti-neoplastic agents. *International journal of cancer* 1998;11:48-51.
- [30] Longo DL. Approach to the Patient with Cancer. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, (eds.) *Harrison's Principles of Internal Medicine*.

New York: McGraw-Hill; 2012. Chapter 81. Available from <http://www.accessmedicine.com/content.aspx?aID=9114033> (accessed August 18 2012).

- [31] kumar R, Marwaha RK, Bhalla AK, Gulati M. Protein energy malnutrition and skeletal muscle wasting in childhood acute lymphoblastic leukemia. *Indian pediatrics* 2000;37(7):720-6.
- [32] Koskelo EK, Saarinen UM, Siimes MA. Skeletal muscle wasting and protein-energy malnutrition in children with a newly diagnosed acute leukemia. *Cancer* 1990;66(2): 373-6.
- [33] Lobato-Mendizábal E, Ruiz-Argüelles GJ, Marín-López A. Leukaemia and nutrition. I: Malnutrition is an adverse prognostic factor in the outcome of treatment of patients with standard-risk acute lymphoblastic leukaemia. *Leukemia research* 1989;13(10): 899-906.
- [34] Shills ME, Young VR. *Modern nutrition in Health and Disease*. Philadelphia: Lea & Febiger;1988. p628.
- [35] Mejía-Aranguré JM, Fajardo-Gutiérrez A, Reyes-Ruiz NI, Bernáldez-Ríos R, Mejía-Domínguez AM, Navarrete-Navarro S, Martínez-García MC. Malnutrition in childhood lymphoblastic leukemia: a predictor of early mortality during the induction-to-remission phase of the treatment. *Archives of medical research* 1999;30(2):150-3.
- [36] Khan AU, Sheikh MU, Intekhab K. Pre-existing malnutrition and treatment outcome in children with acute lymphoblastic leukaemia. *The Journal of the Pakistan Medical Association* 2006;56(4):171-3.
- [37] Rivera-Luna R, Olaya-Vargas A, Velásquez-Aviña M, Frenk S, Cárdenas-Cardós R, Leal-Leal C, Pérez-González O, Martínez-Avalos A. Early death in children with acute lymphoblastic leukemia: does malnutrition play a role? *Pediatric hematology and oncology* 2008;25(1):17-26.
- [38] Pedrosa F, Bonilla M, Liu A, Smith K, Davis D, Ribeiro RC, Wilimas JA. Effect of malnutrition at the time of diagnosis on the survival of children treated for cancer in El Salvador and Northern Brazil. *Journal of pediatric hematology/oncology* 2000;22(6): 502-5.
- [39] Hijiya N, Panetta JC, Zhou Y, Kyzer EP, Howard SC, Jeha S, Razzouk BI, Ribeiro RC, Rubnitz JE, Hudson MM, Sandlund JT, Pui CH, Relling MV. Body mass index does not influence pharmacokinetics or outcome of treatment in children with acute lymphoblastic leukemia. *Blood* 2006;108(13):3997-4002.
- [40] Howard SC, Wilimas JA. Delays in diagnosis and treatment of childhood cancer: where in the world are they important? *Pediatric blood & cancer* 2005;44(4):303-4.
- [41] Slat AM, Egeler RM, van der Does-van den Berg A, Korbijn C, Hählen K, Kamps WA, Veerman AJ, Zwaan CM. Causes of death--other than progressive leukemia--in childhood acute lymphoblastic (ALL) and myeloid leukemia (AML): the Dutch Childhood Oncology Group experience. *Leukemia* 2005;19(4):537-44.

- [42] Lobato-Mendizábal E, López-Martínez B, Ruiz-Argüelles GJ. A critical review of the prognostic value of the nutritional status at diagnosis in the outcome of therapy of children with acute lymphoblastic leukemia. *Revista de investigación clínica* 2003;55(1):31-5.
- [43] Weir J, Reilly JJ, McColl JH, Gibson BE. No evidence for an effect of nutritional status at diagnosis on prognosis in children with acute lymphoblastic leukemia. *Journal of pediatric hematology/oncology* 1998;20(6):534-8.
- [44] Marín-López A, Lobato-Mendizábal E, Ruiz-Argüelles GJ. Malnutrition is an adverse prognostic factor in the response to treatment and survival of patients with acute lymphoblastic leukemia at the usual risk. *Gaceta médica de México* 1991;127(2): 125-31; discussion 131-2.
- [45] Lobato Mendizábal E, Ruiz-Argüelles GJ. [Leukemia and malnutrition. III. Effect of chemotherapeutic treatment on the nutritional state and its repercussion on the therapeutic response of patients with acute lymphoblastic leukemia with standard risk]. *Sangre* 1990;35(3):189-95.
- [46] Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, Hurwitz CA, Moghrabi A, Samson Y, Schorin MA, Arkin S, Declerck L, Cohen HJ, Sallan SE. Improved outcome for children acute lymphoblastic leukemia: results of Dana Farber Consortium Protocol 91-01. *Blood* 2001 Mar 1;97(5):1211-8.
- [47] Hargrave DR, Hann II, Richards SM, Hill FG, Lilleyman JS, Kinsey S, Bailey CC, Chessells JM, Mitchell C, Eden OB; Medical Research Council Working Party for Childhood Leukaemia. Progressive reduction in treatment-related deaths in Medical Research Council childhood lymphoblastic leukaemia trials from 1980 to 1997 (UKALL VIII, X and XI) *British journal of haematology* 2001 Feb;112(2):293-9.
- [48] Metzger ML, Howard SC, Fu LC, Peña A, Stefan R, Hancock ML, Zhang Z, Pui CH, Wilimas J, Ribeiro RC. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. *Lancet*. 2003;362(9385):706-8.
- [49] Gupta S, Bonilla M, Fuentes SL, Caniza M, Howard SC, Barr R, Greenberg ML, Ribeiro R, Sung L. Incidence and predictors of treatment-related mortality in paediatric acute leukaemia in El Salvador. *British journal of cancer* 2009;100(7):1026-31.
- [50] Howard SC, Pedrosa M, Lins M, Pedrosa A, Pui CH, Ribeiro RC, Pedrosa F. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. *The journal of the American Medical Association* 2004;291(20):2471-5.
- [51] Advani S, Pai S, Venzon D, Adde M, Kurkure PK, Nair CN, Sirohi B, Banavali SD, Hawaldar R, Kolhatkar BB, Vats T, Magrath I. Acute lymphoblastic leukemia in India: an analysis of prognostic factors using a single treatment regimen. *Annals of oncology* 1999 Feb;10(2):167-76.

- [52] Nathan PC, Jovcevska V, Ness KK, Mammone D'Agostino N, Staneland P, Urbach SL, Barron M, Barrera M, Greenberg ML. The prevalence of overweight and obesity in pediatric survivors of cancer. *The Journal of pediatrics* 2006 Oct;149(4):518-25.
- [53] Skoczen S, Tomasik PJ, Bik-Multanowski M, Surmiak M, Balwierz W, Pietrzyk JJ, Sztefko K, Gozdzik J, Galicka-Latała D, Strojny W. Plasma levels of leptin and soluble leptin receptor and polymorphisms of leptin gene -18G > A and leptin receptor genes K109R and Q223R, in survivors of childhood acute lymphoblastic leukemia. *Journal of experimental & clinical cancer research* 2011 Jun 1;30:64.
- [54] van Waas M, Neggers SJ, Pieters R, van den Heuvel-Eibrink MM. Components of the metabolic syndrome in 500 adult long-term survivors of childhood cancer. *Annals of oncology* 2010;21(5) 1121-6.
- [55] World Health Organization. WHO: Obesity and Overweight. Fact Sheet N°311. May 2012 <http://www.who.int/mediacentre/factsheets/fs311/en/> (accessed 20 August 2012)
- [56] Nathan PC, Wasilewski-Masker K, Janzen LA. Long-term outcomes in survivors of childhood acute lymphoblastic leukemia. *Hematology/oncology clinics of North America* 2009 Oct;23(5):1065-82, vi-vii.
- [57] Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, Vik TA, Inskip PD, Robison LL. Childhood Cancer Survivor Study. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of clinical oncology* 2003;21(7) 1359-65.
- [58] Lackner H, Schwingshandl J, Pakisch B, Knoblauch S, Mutz I, Urban C. [Endocrinologic function following cranial irradiation in acute lymphoblastic leukemia in childhood]. *Wiener klinische Wochenschrift* 1991;103(19):581-4.
- [59] Janiszewski PM, Oeffinger KC, Church TS, Dunn AL, Eshelman DA, Victor RG, Brooks S, Turoff AJ, Sinclair E, Murray JC, Bashore L, Ross R. Abdominal obesity, liver fat, and muscle composition in survivors of childhood acute lymphoblastic leukemia. *The Journal of clinical endocrinology and metabolism* 2007;92(10):3816-21.
- [60] Diller L, Chow EJ, Gurney JG, Hudson MM, Kadin-Lottick NS, Kawashima TI, Leisenring WM, Meacham LR, Mertens AC, Mulrooney DA, Oeffinger KC, Packer RJ, Robison LL, Sklar CA. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. *Journal of clinical oncology* 2009;27(14):2339-55.
- [61] Ahima RS, Saper CB, Flier JS, Elmquist JK. Leptin regulation of neuroendocrine systems. *Frontiers in neuroendocrinology* 2000 Jul;21(3):263-307.
- [62] Guyton AC, Hall JE. Pituitary hormones and their control by the hypothalamus. In: *Textbook of Medical Physiology*. Philadelphia: Saunders Elsevier; 2011. Chapter 75.
- [63] Ross JA, Oeffinger KC, Davies SM, Mertens AC, Langer EK, Kiffmeyer WR, Sklar CA, Stovall M, Yasui Y, Robison LL. Genetic variation in the leptin receptor gene and obesity in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of clinical oncology* 2004;22(17):3558-62.



- [64] Garmey EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, Yasui Y, Robinson LL, Oeffinger KC. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Journal of clinical oncology* 2008;26(28) 4639-45.
- [65] Gurney JG, Ness KK, Sibley SD, O'Leary M, Dengel DR, Lee JM, Youngren NM, Glasser SP, Baker KS. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. *Cancer*. 2006 Sep 15;107(6): 1303-12.
- [66] Murphy AJ, Wells JC, Williams JE, Fewtrell MS, Davies PS, Webb DK. Body composition in children in remission from acute lymphoblastic leukemia. *The American journal of clinical nutrition* 2006;83(1):70-4.